

Paraneoplastic Pemphigus Developed Shortly after Resection of Follicular Dendritic Cell Sarcoma

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Sir,

Paraneoplastic pemphigus (PNP) is an autoimmune blistering disorder characterized by severe mucosal erosions and polymorphous skin eruptions in association with underlying neoplasia (1). Most cases of PNP are associated with haematological malignancy; however, solid non-haematological neoplasms have also been described in PNP comprising epithelial-origin carcinoma and mesenchymal-origin sarcoma (1, 2). The association of PNP and soft tissue sarcoma is rare; to date approximately 14 cases have been reported (2–5). Of the reported sarcoma cases there have been 4 cases of follicular dendritic cell sarcoma (FDSC) (3). The prognosis of PNP is very poor and may not parallel the treatment of the tumour (1); however, PNP cases associated with benign tumours, such as thymomas and Castleman's tumours, generally showed decreased antibody titre and great improvement of clinical signs following tumour resection (2, 6).

CASE REPORT

A 67-year-old man visited our department with a 4-month history of painful ulcerations on the lips and oral mucosa. The patient also had conjunctival erosions in both eyes, but other

parts of the body were not affected. Eight months earlier, during a routine examination, an incidental mass in the small bowel mesentery was found by abdominal computer tomography (CT) and he underwent complete resection of the mass 4 months later. The tumour was a well-demarcated white-gray-coloured lobulated mass microscopically composed of spindle-shaped cells and dense lymphocytic infiltration with a lesser number of plasma cells and eosinophils (Fig. 1a). The spindle cells were reactive for CD35, smooth muscle actin, leukocyte common antigen, S-100, anaplastic lymphoma kinase and TdT, but negative for CD21, c-kit, CD34, CD31, desmin, epithelial membrane antigen, CD68 and cytokeratin. The infiltrating lymphocytes stained with Ki-67, CD3, CD20 and CD30. Oral and conjunctival blisters were first observed several days after tumour resection, and one month after surgery progressive ptosis and dysphagia also developed. He was diagnosed with myasthenia gravis (MG). Thymoma was ruled out based on a chest CT scan. Treatment with prednisolone, azathioprine and pyridostigmine bromide was initiated, but during the course of treatment, the oral lesions worsened and he was referred to our hospital. Physical examination revealed extensive erosions and ulcerations of the buccal mucosa, tongue and lips (Fig. 1b). Conjunctival erosions and scarring were shown, but, no skin lesions were noted. Biopsy from the buccal aspect of the lower lip and conjunctiva revealed vacuolization of basal cells with suprabasilar acantholytic cleft (Fig. 1c, d). Direct immunofluorescence (IF) revealed weak deposition of IgG and C3 at the basement membrane zone. Indirect IF showed a typical circulating IgG that bound to the

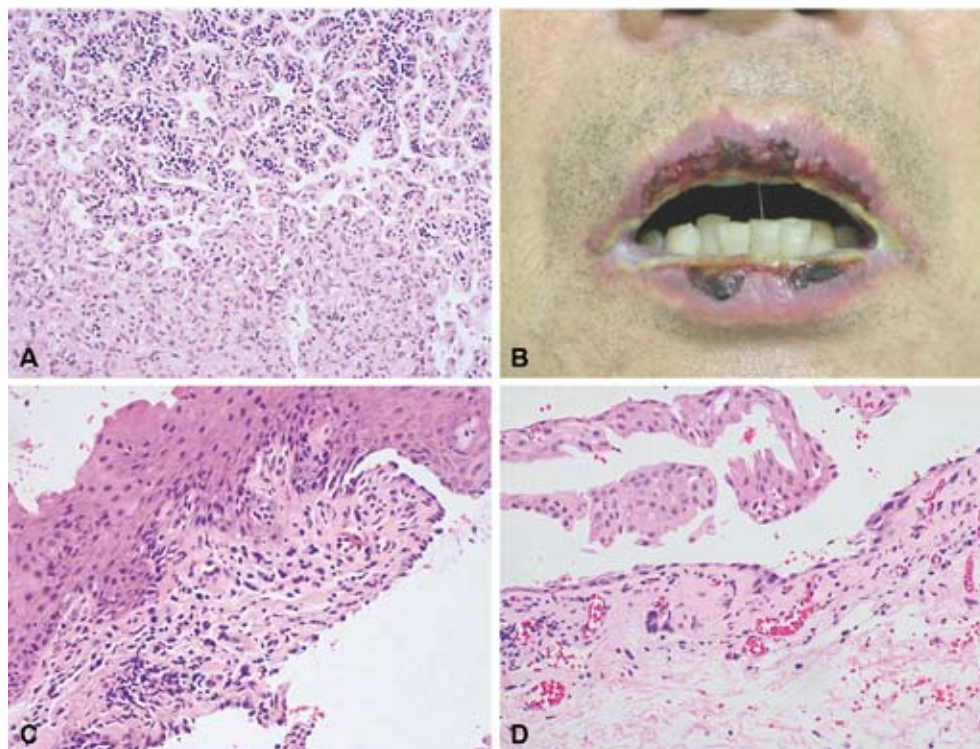


Fig. 1. (a) Histopathological features of the tumour show proliferation of spindle cells in a myxoid stroma and dense inflammatory cells, mainly lymphocytes and a few plasma cells (haematoxylin and eosin; H&E $\times 200$). (b) Ulcerations and hemorrhagic crusts on the oral mucosa and both lips. (c) Biopsy from oral lesions shows vacuolization of basal cells with suprabasilar acantholytic cleft (H&E $\times 200$). (d) Acantholysis of the basal layer in the form of a "row of tombstones" in the epidermis of conjunctival lesions (H&E $\times 200$).

surface of keratinocytes at a titre of 1:160 on normal human skin. Desmoglein (Dsg) enzyme-linked immunoassay (ELISA) showed negative results for Dsg1 and Dsg3. Immunoblotting analysis using normal human epidermal extracts detected the 210-kDa envoplakin and 190-kDa periplakin, confirming the diagnosis of PNP (Fig. 2). Oral prednisolone, 40 mg daily and cyclosporine, 200 mg daily and intravenous immunoglobulin 2 g/kg daily for 5 days resulted in an improvement in the oral and conjunctival mucosal lesions. The symptoms of MG also improved, and follow-up examination for acetylcholine receptor binding antibody showed a serum level elevated by 7.276 nmol/l and the acetylcholine receptor blocking antibody was positive by 38.5%. At one year after tumour resection, multiple liver metastasis were found during follow-up. The haematoxylin and eosin histological features of the metastatic tumour were similar to those of the primary tumour, with spindle-shaped cells with dense lymphocytic infiltration, but the immunohistochemical findings were CD35- and CD21-positive. Several pathologists confirmed these immunohistochemical findings and concluded that the final diagnosis of the tumour was FDCCS.

DISCUSSION

The patient developed oral and conjunctival ulcerations and MG shortly after the associated tumour resection, and the lesions were exclusively limited to the mucous membranes without skin involvement. In addition, Dsg ELISA showed negative results for both Dsg1 and Dsg3. However, our patient demonstrated antibodies against 210-kDa envoplakin and 190-kDa periplakin on immunoblotting. According to the modified version of the diagnostic criteria suggested by Camisa & Helm (7), our patient fulfils three major criteria, the polymorphous mucocutaneous eruption, concurrent internal neoplasia, and the immunoblotting results that detected both 210-kDa envoplakin and 190-kDa periplakin, which are the most characterized and consistently recognized antibodies of PNP, confirming the diagnosis of PNP.

The most unusual clinical feature of our patient is development of mucosal and conjunctival erosions and MG shortly after the tumour resection. Wang et al. (8) demonstrated that B-cells in Castleman's tumour produced autoantibodies against the plakins family and Dsg3 in a patient with PNP, and recently other tumours associated with PNP such as thymomas and FDCCS were also reported to have B-cell clones producing autoantibodies (3). Therefore, it may be possible that the operation itself triggered the antibody production from the B-cells of FDCCS or haematogenous spread of antibody-producing tumour cells in our patient. If this hypothesis is true, extremely careful resection is necessary to prevent stimulation or dissemination of antibody-producing tumour cells.

Another unusual clinical finding in our case was that the lesions were limited exclusively to the oral and conjunctival mucosa without skin involvement. Although the oral mucosa is involved in all cases of PNP, it is very rare for the lesions to be limited to the mucosa (2). To our knowledge there have been two reported cases that showed limited mucosal involvement (9, 10).

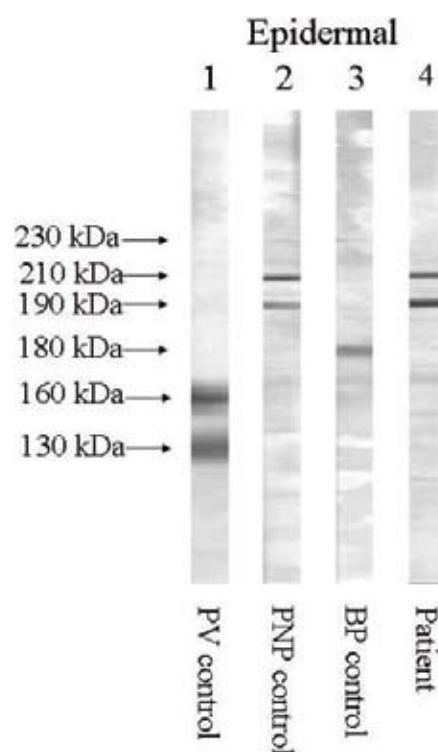


Fig. 2. Immunoblot analysis of human epidermal extracts. Control pemphigus vulgaris (PV) serum reacted with the 160-kDa anti-desmoglein (Dsg)1 and 130-kDa Dsg3 (lane 1), control bullous pemphigoid (BP) serum reacted with BP 230 and BP 180 (lane 3), and control paraneoplastic pemphigus (PNP) serum reacted with the 210-kDa envoplakin and the 190-kDa periplakin (lane 2). The patient serum detected envoplakin and periplakin (lane 4).

Amagai et al. (11) suggested that most patients with PNP have Dsg3 autoantibodies and that the antibody plays a pathogenic role in PNP. However, in our patient, the mucosal lesions showed suprabasal acantholysis similar to pemphigus vulgaris, but the Dsg ELISA was negative for Dsg3. One possible explanation for this unusual feature is that the titre of anti-Dsg3 antibodies in our patient may be too low to be detected by ELISA. Another possibility is that the acantholysis in our patient may have been induced by antibodies against epithelial proteins other than Dsg3. Several case reports have shown PNP patients with negative results in Dsg ELISA (12, 13). In spite of the absence of anti-Dsg3 IgG, patients showed clinical manifestations of PNP. In addition to the PNP antigenic complex, other target epithelial antigens and their specific roles in the pathophysiological mechanisms of PNP remain to be discovered.

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